Journal of Current Hematology & Oncology Research

Review

DOI: 10.51271/JCHOR-0065

The role of ELABELA in targeted treatment of acute myeloid leukemia

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Cite this article: Yanardağ Açık D, Karabulut ZT. The role of ELABELA in targeted treatment of acute myeloid leukemia. *J Curr Hematol Oncol Res.* 2025;3(3):67-73.

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Received: 16/05/2025 ◆ **Accepted**: 24/10/2025 ◆ **Published**: 08/08/2025

ABSTRACT

Acute myeloid leukemia is a clonal stem cell disease. Various molecular targets are being sought in this disease which has a low chance of cure. However, it is desired that targeted treatments should have few side effects. We tried to understand whether the embryogenic peptide ELABELA, which has been closely associated with many pathways involved in cancer mechanism, is a peptide worth investigating in targeted treatment of acute myeloid leukaemia.

Keywords: ELABELA, acute myeloid leukemia, cellular pathways, targeted therapy, new peptide

INTRODUCTION AND OVERVIEW OF ACUTE MYELOID LEUKEMIA (AML)

Acute myeloid leukemia (AML) is a genetically, epigenetically and clinically heterogeneous disease characterized by the accumulation and expansion of immature myeloid cells in the bone marrow (BM) and peripheral blood (PB), resulting in failure of normal hematopoiesis.[1]

Morphological heterogeneity of AML arises from the diversity of genotypes seen.[2]

As in other cancers, various intracellular and extracellular signaling pathways, proteins, peptides, receptors etc. in these pathways play a role in the pathogenesis of AML. Although blocking and inhibition of some molecules involved in these complex pathways have led to important developments in cancer treatment, the results are still unsatisfactory.[3-5]

CANCER STEM CELLS (CSCS) AND THEIR ROLE IN AML

Cancer stem cells (CSCs) are responsible for cancer recurrence, metastasis and resistance to treatment, especially in leukemias. The activities of CSCs are controlled by many intracellular and extracellular factors and these factors can be used as drug targets for cancer therapy. CSCs have been initially identified in leukemia. CSCs can generate tumors through self-renewal and differentiation into multiple cellular subtypes.[6-11]

ELABELA: A NOVEL PEPTIDE IN EMBRYOGENESIS AND CANCER

During embryogenesis, apela (ELABELA/ELA/Toddler) and apelin receptor (AR) mRNA expression is increased, leading to apela-AR signaling that facilitates the migration of progenitor cells to the anterior lateral plate mesoderm via Nodal/TNFβ-dependent signaling for proper cardiovascular development in zebrafish.[12-14] However, following this, apela levels rapidly decrease and apelin mRNA levels increase.[15] CSCs and normal stem cells share some of the same regulatory signaling pathways such as Wnt/β-catenin, Sonic Hedgehog (Hh), and Notch pathways involved in the self-renewal process.[16-18] Targeting these common pathways may result in complications such as profound cytopenia and BM failure. Therefore, finding targets that have lost their functions after the embryonic period, but reappear or persist in possible CSCs will be advantageous in destroying the cancer stem cell, and even if this does not happen, it will be advantageous in protecting against the side effects of treatment. One of these targets may be Apela peptide, which has lost its function after the embryonic period but is abundantly expressed in embryonic stem cells[12-14] and has been shown to be expressed in some cancer cells in recent studies.[19-21]

Apela binds to an unknown receptor different from apelin in ESCs, inhibits apoptosis of stem cells and stimulates self-renewal. Apela may have varying effects on ESCs derived from different species. Human and murine pluripotent ESCs respond differently to exogenous apela treatment. In human ESCs, it inhibits apoptosis.[22] In mice, apela can cause apoptosis in a non-peptidic manner.[23]

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In this paper, we examine whether ELABELA, a peptide that has an important role in signaling pathways involved in AML mechanism and especially in ESC, is worth investigating in targeted treatment.

Wnt signaling is required for the sustainability of leukemic stem cells. Several molecules involved in or modulating Wnt signaling have a prognostic value in AML. These include: β-catenin, LEF-1, phosphorylated-GSK3β, PSMD2, PPARD, XPNPEP, sFRP2, RUNX1, AXIN2, PCDH17, CXXC5, LLGL1, and PTK7.[2]

From a successful treatment perspective, the cancer stem cell model implies that the LSC population must be eliminated to eradicate the disease and achieve long-term remissions.[24]

Notch-, Wnt- and Hedgehog signaling pathways are particularly important for LSC biology.[25]

Numerous lines of evidence suggest that abnormal WNT signaling may also impair cancer immune surveillance, thereby stimulating immune escape and resistance to various immunotherapies, including immune checkpoint blockers.[26,27]

Both p53 and the Wnt signaling pathway play important roles in regulating the differentiation of mouse embryonic stem cells (mESCs). Lee et al.[27] identified the Wnt signaling pathway as one of the main targets of p53 in mESCs.

Glycogen synthase kinase-3 (GSK-3) and protein phosphatase 2A (PP2A) are two important signaling molecules involved in AML pathogenesis and MYC stability. GSK-3β is involved in the regulation of cell metabolism, cell differentiation, apoptosis, autophagy and tumorigenesis of leukemia. PP2A is a serine/threonine phosphatase that suppresses tumor growth and regulates kinase-directed intracellular signaling pathways.[29]

Takam Kamga et al.[29] have shown that pharmacological interference via small molecule inhibitors of Wnt and/or GSK-3 signaling reduces AML cell survival by sensitizing leukemia cells to chemotherapeutic agents both in vitro and in vivo.

The G protein-coupled chemokine receptor CXCR4 is specifically associated with cancer metastasis and HIV-1 infection.[31] The chemokine receptor, CXC receptor 4 (CXCR4), with its ligand chemokine ligand 12 (CXCL12), plays a key role in the survival and migration of normal and malignant stem cells into the BM. High CXCR4 expression in AML and ALL blasts has been shown to be an indicator of poor prognosis for these diseases. Several small molecule inhibitors, short peptides, antibodies and antibody drug conjugates have been developed to more effectively target and kill malignant cells expressing CXCR4. Apelin and apela are two peptide ligands for a class A G-protein coupled receptor (GPCR) called the AR (AR/APJ/APLNR). They function by binding to this receptor, and this is known as the Apelinergic system (Apelin/APJ system). Binding of both endogenous peptides to the AR produces similar physiological effects. The AR transmembrane (TM) domain is highly homologous to the chemokine receptors CXCR4 and CCR5.[15,32]

Apelin peptides (apelin and ELABELA) and the GPCR of the same origin, known as the apelin receptor (Aplnr), play key roles in apoptosis, cell proliferation, angiogenesis, metabolic disorders and various cancers.[33,34] The CXCR4 receptor interacts with CXCL12 (SDF-1) generated by BM endothelial and stromal cells, including CXCL12-bol reticular (CAR) cells. Therefore, CXCR4 may be an attractive molecular target for the treatment of these malignancies. Studies have shown that increased CXCR4 expression is correlated with poor results in patients with AML and B-cell ALL. This is potentially due to the role of CXCR4 in retaining leukemic cells within the BM and their role in activating pathways that support the survival, growth and chemotherapy resistance of these malignant cells. In AML cases, leukemic blasts with high CXCR4 expression have been associated with higher relapse rates and lower overall survival. Patients with FMS-like tyrosine kinase-3 internal tandem duplication (FLT3-ITD) or nucleophosmin mutation have significantly higher CXCR4 expression than their wild-type counterparts. The CXCR4 receptor plays a crucial role in leukemia maintenance through several mechanisms, including survival signaling and retention of leukemia cells in the protective BM niche.[35-44] LSCs are tumor-initiating cells that are resistant to standard chemotherapy and promote the persistence and relapse of AML.[45]

CXCL12 antagonists are designed to disrupt the CXCR4/CXCL12 axis and sensitize malignant cells to chemotherapy.[35] Of the CXCL12 antagonists, successful treatment has only been achieved with CX-01.[46]

In apoptosis, the B-cell lymphoma protein 2 (Bcl-2)-associated X (Bax) protein releases cytochrome c from mitochondria, activating a cascade of reactions that assists the successive activation of caspases and ultimately leads to cell death. Bcl-2 is believed to inhibit Bax's release of cytochrome c, thereby restricting the downstream activation of the apoptotic machinery. Both Bax and Bcl-2 are cytoplasmic proteins.[47] BCL2 is thought to mediate resistance to standard treatment in patients with unfavorable risk AML.[48]

Mutation of the tumor suppressor gene TP53 is associated with poor prognosis in AML. The TP53 gene is largely a stress response protein with functions ranging from apoptosis to cell cycle control. The fate of the p53 protein in the cell is mainly determined by the rate of degradation rather than the rate of generation. p53 is mainly degraded by the interaction of p53 with MDM2 (double minute 2 protein). This coupling of p53/MDM2 can be disrupted when stress or DNA damage is detected, resulting in the stabilization of p53. Overexpression of MDM2 leads to deactivation of p53.[49,50] MDM2 and MDM4 are negative regulators of TP53 activity targeting degradation via ubiquitination. In AML, MDM2 is frequently overexpressed, so cells can have low functional TP53 activity without TP53 deletion/mutation. Nutlin-3a is a small molecular inhibitor of MDM2/p53 interaction, thus this therapeutic provides increased p53 levels secondary to reduced p53 degradation and consequently up-regulates

apoptosis.[50,51] It has been suggested that Venetoclax plus idasanutlin may be an effective treatment for relapsed/refractory AML.[52]

Apelin and apela are two peptide ligands for a class A GPCR called the AR. They function by binding to this receptor, and this is known as the apelinergic system (apelin/APJ system). Coupling of both endogenous peptides to the AR produces similar physiological effects. It is well known that the apelin/APJ system can regulate apoptosis in various cell types, subsequently mediating the occurrence and development of associated diseases. Recent evidence suggests that the Apelin/APJ system affects apoptosis in various diseases through different signaling pathways in different disease pathways. Pretreatment of cardiomyocytes with a pelin-13 effectively prevents apoptosis induced by glucose deprivation (GD) and can significantly increase Akt and mTOR phosphorylation by positive regulation of Bcl-2 protein and negative regulation of Bax and cleaved caspase-3. The apelin/APJ system also increases the expression of Bcl-2 and decreases the expression of Bax protein.[53-57] Inhibition of the apela or apelinergic system will show the effect of both venotoclax and idasanutline together.

Apela functions as an endogenous ligand for the GPCR, APLNR, and Apela and APLNR have been shown to direct angioblast migration to control vascular patterning in zebrafish embryos.[14,58,59]

MOLECULAR MECHANISMS LINKING ELABELA TO AML

Apela is predicted to bind to a different receptor than apela.[15] Apela is highly expressed in human blastocysts before implantation and contributes to human embryonic stem cell (hESC) pluripotency through an alternative receptor. In a study in human pluripotent embryonic stem cells (ESCs), apela inhibited cell apoptosis and stimulated self-renewal. However, these undifferentiated stem cells did not express AR. Only after differentiation, about three days later, AR expression was detected.[22] This is highly suggestive of the existence of an additional, as yet unknown receptor for apela and indicates that apela is involved in pluripotent stem cells prior to and independent of AR formation. In this case, targeting apela in the treatment of AML, or at least in the preparatory regimen for hematopoietic stem cell transplantation, will perhaps enable cancer stem cell targeting.

The non-coding region of Apela has been shown to be involved in the regulation of p53-mediated DNA damage-induced apoptosis in mouse embryonic stem cells (mESCs). Apela negatively regulates the interaction between heterogeneous nuclear ribonucleoprotein L (hnRNPL) and p53.[23] Seo et al.[59] showed that DNA damage-induced hnRNP L positively regulates p53 expression. Li et al.[22] have shown that Apela negatively regulates the interaction between hnRNPL and p53, resulting in an antiapoptotic effect. Yi et al.[19] showed that apela expression was high in ovarian cancer cells. Disruption of apela expression in these cell lines suppressed cell growth, cell migration and cell cycle progression. They showed that apela demonstrated this effect independently of APLNR and affected cell growth and cell cycle progression in a p53-dependent way. Loss of apela in high p53-expressing cells caused a decrease in cell number due to cell death, which was caused by p53-induced cell apoptosis.

Mouse double minute2 (MDM2) is a critical negative regulator of the tumour suppressor p53, which plays a key role in controlling its transcriptional activity, protein stability and nuclear localization. MDM2 expression is upregulated in many cancers, resulting in loss of p53-dependent activities such as apoptosis and cell cycle arrest.[61]

The PI3K/Akt signaling pathway has been shown to play a critical role in tumorigenesis of hematopoietic cells. Activation of the PI3K/Akt pathway occurs even in the early stages of tumors and is correlated with poor prognosis and therapeutic resistance in various human cancers.[22,62]

Mammalian target of rapamycin (mTOR) is an evolutionarily conserved kinase in eukaryotes that plays a critical role in sensing and responding to factors such as nutrient availability, energy sufficiency, stress, hormones and mitogens. mTOR forms two complexes, referred to as mTOR complex 1 (mTORC1) and mTORC2. mTORC1 also regulates mitochondrial biogenesis and autophagy.[63-66] Hoshii et al.[66] in their study revealed that mTORC1 is required for leukemia initiation.

The phosphatidylinositol-3-kinase (PI3K)/Akt/mTOR pathway are two pathways that are crucial for many aspects of cell growth and survival in cancer as well as physiological.[68]

GSK3β functions as a link between the PI3K/mTOR and WNT/β-catenin pathways through AMP-activated protein kinase (AMPK).[69,70]

AMPK activation leads to inhibition of mTORC1 by two independent mechanisms: activation of the negative mTORC1 regulator tuberous sclerosis complex 2 (TSC2) and inhibition of the mTORC1 sub-unit RAPTOR.[71-73] c-Myc is an essential transcription factor that plays a convincing role in leukemogenesis. In vitro and in vivo studies have suggested that higher expression of c-Myc is correlated with the progression of AML.[74] Two key regulators of c-Myc are glycogen synthase kinase 3beta (GSK-3β) and PP2A.[29] GSK-3β is involved in the regulation of cell metabolism, cell differentiation, apoptosis, and autophagy and leukemia tumorigenesis.[75] GSK-3β is also involved in leukemia survival, chemotherapy resistance and body protection.[76] GSK-3β is a vital tumor suppressor.[77] In its tumor suppressor function, GSK-3β regulates Wnt signaling to passivate inhibitory phosphorylation of β-catenin and prevents cell cycle progression.[78] Soulet et al.[78] demonstrated the effects of ELA on autophagy and mTORC1. They showed that ELA is also involved in the regulation of the expression of mTORC1 network proteins and autophagy. They identified ELA as an important positive regulator of mTORC1.

Apela stimulates hESC cell cycle progression and protein translational by activating PI3K/AKT/mTORC1 signaling and blocks stress-induced apoptosis. These pathways are the main signals reported to correlate with apoptosis. MDM2 also inhibits p53 through this pathway. It is predicted that the apelinergic system may inhibit apoptosis through these

common pathways (53- 57). hnRNPC is a negative regulator of p53. It was also shown that the 1-41 p53 region, the region where p53 binds to MDM2, interacts with hnRNPC. These results showed that hnRNPC may be synergistic with MDM2 in regulating p53 stability. Doxorubicin competes with p53 for binding to the RNA recognition motif of hnRNPC, thereby increasing p53 stability and inducing p53-dependent apoptosis.[80] Chemokines are produced by cancer-associated fibroblasts, a component of stromal cells, and affect the metastatic potential and region-specific spread of cancer cells. Stromal-derived factor-1 (SDF-1/CXCL12) belongs to the CXC chemokine family. The effects of CXCL12 in many cancers have been described, including its role in promoting local invasion and distant lung cancer metastasis.[81-83] Wang et al.[83] in their study showed that CXCL12 blocks apoptosis in human adenocarcinoma cell line via CXCR4. They observed that the expression levels of Bcl-2 and bcl-xl in the adenocarcinoma cell line were increased by treatment with CXCL12 and decreased by CXCR4 antagonist and JAK2 inhibitor. Apela, which has been shown to be antiapoptotic, has also been shown to interfere with the chemokine CXCR4a signaling pathway.[22]

In summary, apela and apelinergic system has been shown to inhibit apoptosis in many steps (via bcl-2, bcl-xl, mdm2, hnRPLN, p53, PI3K/Akt/mTORC1, chemokines). Based on these results, we can say that apela and the apelinergic system occupy a central position in leukaemia.

AKT, ERK and mTOR kinases form a complex pathway that regulates various cellular functions, most prominently cell growth, migration and survival.[79]

AML LSCs (leukemia stem cells) maintain naturally high mitophage activity through AMP-activated protein kinase (AMPK) activation to maintain a low physiological state of reactive oxygen species (ROS), which is critically required for the preservation of their self-renewal potential.[85]

Autophagy is frequently activated in cancer and is largely associated with metabolic reprogramming and oncogenesis. Autophagy (i.e. lipophagy) has been shown to participate in lipid catabolism to supports OxPHOS, i.e. to maintain energy metabolism by delivering free fatty acids (FFAs) to mitochondria via degradation of lipid droplets (LD) in AML cells but not in normal hematopoietic cells. Autophagy supports OXPHOS, whereas inhibition of OXPHOS reduces autophagic flow.[86]

Autophagy is thought to inhibit cancer development. Conversely, once cancer has formed, increased autophagic flow often provides tumor cell survival and growth.[87-89] In other words, autophagy has different effects on cancer formation and progression. Therefore, both inhibition and activation of autophagy can be used in treatment.[87,88]

mTORC1 stimulates biosynthetic pathways, including the synthesis of proteins, lipids and nucleotides, and promotes cell growth by inhibiting cellular catabolism through suppression of the autophagic pathway. However, inhibition of autophagy initiates cancer formation. So mTORC1 probably contributes to the development of AML. Altman et al.[90] have demonstrated the antileukemic effects of blocking mTORC1 and mTORC2 in cell culture studies. However, mTORC1 negatively regulates and inhibits autophagy. Inhibition of autophagy in AML is among the treatment targets.[90-92]

Soulet et al.[78] showed that ELA plays a role in the regulation of the expression of mTORC1 network proteins. They showed that ELA activates mTORC1 and this activation inhibits autophagy. They also showed that the effect of ELA on autophagy is abolished in the absence of mTORC1 expression. ELA has been shown to be an important positive regulator of mTORC1. This correlation may suggest that mTORC1 and ELA may be jointly responsible for the initiation of AML.

BCL-2 inhibitors (venetoclax) inhibit oxidative phosphorylation (OXPHOS) in leukemic stem cells (LSC) and lead to cell death. Inhibition of OXPHOS reduces autophagic flow.[86]

ELABELA AND POTENTIAL THERAPEUTIC TARGETING IN AML

Targeting apela, which seems to be almost central to the cancer pathways involved in AML, is promising. However, cell culture studies will be very valuable to see the real effect of apela and will reveal more real results. Although blocking/inhibiting Apela seems logical according to the pathways it is involved in and the results of the studies, it is also possible to encounter a different result in cell culture studies. For example, Soulet et al.[78] reported that sunitinib and ELA showed synergistic effects in suppressing tumor growth and angiogenesis in mice. In the same study, they found that APELA expression was upregulated in colon, lung, stomach and thymoma cancers, but did not change in other cancer tissues analyzed except kidney cancer tissues, while APLN and APLNR expression was upregulated in clear cell renal carcinoma (ccRCC) and downregulated in papillary renal cell carcinoma (RCC). In other words, the expression of apela and APLNR differs in different cancer types; therefore, inhibition or induction of APLNR is likely to show different effects in different cancer types. Sunitinib (SU11248) is a small molecule FLT3 inhibitor with selectivity for PDGFR, VEGFR1, VEGFR2, KIT, and FLT3. It has both direct anti-tumor and antiangiogenic properties. The use of sunitinib is currently approved for the treatment of renal cell carcinoma, gastrointestinal stromal tumor and AML.[93] Cell culture studies will be valuable to understand whether this synergistic effect is observed in AML.

CONCLUSION

As a result, many molecules and cancer pathways involved in AML formation have a close connection with Apela. Therefore, Apela seems to be a peptide worth investigating in AML treatment. Cell culture studies and later phase studies will provide valuable information to the literature.

ETHICAL DECLARATIONS

Referee Evaluation Process

Externally peer-reviewed.

Conflict of Interest Statement

The authors have no conflicts of interest to declare.

Financial Disclosure
The authors declared that this study has received no financial support.

Author Contributions
All of the authors declare that they have all participated in the design, execution, and analysis of the paper, and that they have approved the final version.

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